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In re Application of:	
David Dakin Iorwerth WRIGHT et al.	Group Art Unit: 1616
Application No.: 10/522,527	Examiner: Soroush, Ali
Filed: October 10, 2006	
For: THERAPEUTIC FOAM	Confirmation No.: 7497

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, Janet RUSH, do hereby make the following declaration:

1. I am the Senior Vice President of Medical and Regulatory Affairs, US at BTG International Inc ("BTG").

2. I have been awarded an M.D. by Ohio State University, and completed medical residency at Boston Medical Center. I am Board Certified in Internal Medicine, licensed to practice medicine in the state of Pennsylvania, and a Certified Physician Investigator (Academy of Pharmaceutical Physicians and Investigators). For the past 25 years I have been engaged in pharmaceutical clinical research and regulatory affairs at Merck, Aventis, and BTG. I have filed 5 New Drug Applications for new molecular entities leading to worldwide approvals.

3. During my employment at BTG, I have been engaged in the clinical research of the treatment of varicose veins. I am currently the Medical Monitor of a US Phase II safety study of a sclerosing foam treatment of varicose veins.

4. Given my education and experience as the Medical Monitor of the current clinical trial, I consider myself able to provide the following testimony based on experiments and procedures conducted by me, under my supervision or by colleagues.

5. Since the late 1990s, foams made with a liquid sclerosant and air have been widely used to treat varicose veins in the U.S. and in Europe.

6. A study by Eckmann et al (Dermatol. Surg. June 2005; 31(6): 636-43), however, demonstrated that a sclerosant foam made with air could block the circulation of blood in rat cremaster vessels after injection of the foam into the rat circulatory system.

7. In 2001-2003, a phase III clinical trial of a sclerosing foam treatment using a foam made with carbon dioxide and oxygen with a 7% nitrogen content ("old Varisolve® foam") was conducted in Europe. The old Varisolve® foam was compared to a variety of sclerosing foams made with atmospheric air. Consistent with each investigator's usual practice the air foams were administered in smaller volumes (median 9.8ml for room air foam and 18.9ml for Varisolve®). In my opinion, it was nevertheless unexpected that the old Varisolve® foam containing only 7% nitrogen caused transient neurological and visual effects in 6 out of 437 (1.4%) patients compared with 1 out of 125 (0.8%) patients treated with foam made with room air.

8. In the Eckmann study, there was also a visible difference in the number of bubbles circulating in rat cremaster vessels after injecting the old Varisolve® foam as

compared to a foam made with carbon dioxide and oxygen and a nitrogen content of less than 0.8% (new Varisolve® foam). Surprisingly, injecting the old Varisolve® foam resulted in visible bubbles in rat cremaster vessels, while injecting the new Varisolve® foam resulted in virtually no bubbles. Specifically, with a foam containing 7% nitrogen, there were visible bubbles in 5 out of the 6 animals tested, and with a foam containing less than 0.8% nitrogen, there were visible bubbles in 1 out of the 6 animals.

9. As recently explained in my submission to the New England Journal of Medicine (Appendix 1), the current US Phase II safety study in which I am Medical Monitor is investigating whether treatment with foam with less than 0.8% nitrogen gas (new Varisolve® foam) can cause subclinical events such as microinfarctions in the brains of varicose vein patients with right-to-left (R-L) cardiac shunts.

10. It is thought that R-L shunts, e.g. patent foramen ovale, allow bubbles to enter the brain by crossing from the venous into the arterial circulation.

11. The current study will conclude when 50 patients with bubbles detected in the middle cerebral artery (MCA) of the brain have been treated and followed up at 24 hours and 28 days using MRI scanning and other procedures.

12. In the study, if a patient experiences visual disturbances or neurological symptoms it is recorded. Any symptoms occurring within the first 24 hours after treatment are considered potentially relating to treatment. We were prepared for patients to experience visual and neurologic effects as the protocol specifies actions to be taken if this occurs.

13. However, of the 87 patients administered the new Varisolve® foam in the ongoing study and a previous study, 42 of which had bubbles detected in the MCA,

none displayed visual disturbances or neurological symptoms within the first 24 hours after treatment.

14. By comparison, of the 534 patients treated to date with old Varisolve® foam, (7 % nitrogen gas), 9 patients, or 1.7%, displayed visual disturbances or neurological symptoms within the first 24 hours after treatment.

15. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: April 29, 2008

By: Janet G Rush
Dr. Janet RUSH

The NEW ENGLAND JOURNAL of MEDICINE

SUBMIT A LETTER TO EDITOR
ABOUT A RECENT *JOURNAL* ARTICLE

The letter will not be submitted until you click the submit button at the bottom of this page.

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4/3/2008

Article Referenced:
- Correspondence - Microembolism during Foam Sclerotherapy of Varicose Veins

To the Editor:

Ceulen(1) found intracardiac gas emboli in all patients treated with polidocanol foam (air-to-liquid ratio 4:1), noting potential for microembolism. We corroborate this observation with a 45-patient series treated with proprietary very-low-nitrogen (<0.8%) polidocanol microfoam (Varisolve®) generated via a sterile canister system controlling bubble size. In our unpublished series intracardiac gas emboli were detected in all patients. A multicenter IND trial is ongoing in patients with great saphenous vein incompetence and R-L cardiac shunts to investigate the clinical significance of gas emboli with the proprietary very-low-nitrogen microfoam. On pre-treatment screening, the prevalence of R-L shunt was unexpectedly high (40%). During treatment, 36 patients had cerebral emboli detected by transcranial Doppler and underwent extensive monitoring including diffusion weighted MRI at 24 hours and 28 days. No cerebral lesions were detected, and no abnormalities noted on perimetry or cardiac markers.(2) The study will continue until 50 patients with cerebral emboli are studied. In contrast, the risk of physician-compounded room-air foams is difficult to quantify in the absence of specific data on the potential for cerebral infarction.

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Word count is 174

Disclosure:

Drs. Rush and Wright are employees of BTG International, the company developing the proprietary

microfoam Varisolve(R) under an IND.

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1. Ceulen RPM, Sommer A, Vernooy K. Microembolism during foam sclerotherapy of varicose veins. N Engl J Med 2008;358:1525-26.
2. Regan JD, Gibson KD, Ferris B, et al. Safety of proprietary sclerosant microfoam for saphenous incompetence in patients with R-to-L shunt: Interim Report. J Vasc Interv Radiol 2008; 19:S35 (meeting abstract).

Microembolism during Foam Sclerotherapy of Varicose Veins

TO THE EDITOR: Chronic venous insufficiency is a common disease in adulthood. One recently developed therapy for varicose veins is foam sclerotherapy.[1]

We used foam sclerotherapy in a 51-year-old man and a 33-year-old woman who had symptomatic varicose great saphenous veins and were otherwise healthy. Immediately after the initiation of treatment, transient scotomas developed in the man, and a migraine attack in the woman.

On the basis of these observations, we decided to monitor by echocardiography the foam distribution during foam sclerotherapy in 33 consecutive patients with chronic venous insufficiency. The treatment in each patient was carried out according to European consensus guidelines.[2] Briefly, patients received a single injection of 5 ml of 1% polidocanol foam (air-to-liquid ratio, 4:1). The foam was injected with the patient's leg slightly elevated, while the saphenofemoral junction was manually compressed until full vasospasm occurred and blood-flow velocity in the great saphenous vein decreased to zero.

In all patients studied, we detected foam microemboli in both the right atrium and ventricle between 45 seconds and 15 minutes after foam injection (Fig. 1A). In five patients, microembolism was also detectable in the left atrium and ventricle (Fig. 1B); however, neurologic signs did not develop in any of them. Careful echocardiographic examination of these five patients showed a right-to-left shunt through a patent foramen ovale. Because the neurologic symptoms observed in the two index patients could have reflected adverse effects of foam sclerotherapy due to a right-to-left shunt, we subsequently examined both patients by echocardiography and detected a patent foramen ovale in each.

These findings suggest that foam-induced microembolism is a common phenomenon during foam sclerotherapy. The prevalence of patent foramen ovale, which can be a source of paradoxical embolism, is approximately 26% in the general population.[3] Still, serious neurologic symptoms after foam sclerotherapy, which include scotomas, migraine, and stroke, occur in only 2% or less of patients.[4,5] Thus, the findings in our cohort are in line with previous reports. Although the overall number of neurologic adverse

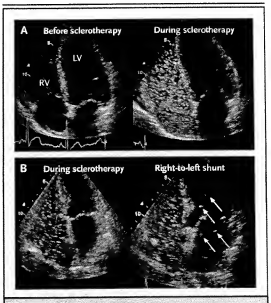

Figure 1. Echocardiographic Images Obtained during Sclerotherapy with Foam Injection.

Panel A shows apical four-chamber images before and during foam sclerotherapy. Foam microemboli are present in the right atrium and ventricle of the heart. Panel B shows paradoxical foam microembolism during foam sclerotherapy. Microemboli in the left atrium and ventricle of the heart (arrows) are due to a right-to-left shunt through a patent foramen ovale. RV denotes right ventricle, and LV left ventricle.

effects during foam sclerotherapy might be underestimated, it appears that neurologic complications develop in relatively few patients with right-to-left shunts and foam microembolism.

Nevertheless, we suggest that caution be exercised when foam sclerotherapy is performed in patients with a known patent foramen ovale and that patients with overt neurologic symptoms undergo an additional echocardiographic examination for the presence of a patent foramen ovale. Further prospective studies are needed to evaluate and confirm our observations.

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CONCLUSION: The stability of STD foam can be markedly enhanced by the addition of ethiodized oil. For 3% STD (the concentration most often used in large veins), a five-fold increase in foam duration was achieved by adding ETO at the relatively modest ratio of 9:1.

2:12 PM **Abstract No. 87**

Safety of Proprietary Sclerosant Microfoam for Saphenous Incompetence in Patients with R-to-L Shunt: Interim Report.

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PURPOSE: In patients treated with IV sclerosant foams, circulating gas bubbles reach the right heart and are usually filtered out by the lung. In patients with right-to-left (RL) shunts, bubbles may enter the arterial circulation. It is unknown whether these bubbles can cause microvascular infarctions. This study investigates whether patients with MCA bubbles detected during treatment with a proprietary polidocanol microfoam (MF) experience subclinical events.

MATERIALS AND METHODS: Patients with SFJ incompetence and great saphenous vein (GSV) reflux (CEAP 3-5) who are ≤ 60 years and free of arteriovascular disease can be enrolled in this IND study. Transcranial Doppler (TCD) with agitated saline contrast assesses presence of RL shunt prior to treatment. GSV incompetence is treated by injection of a proprietary polidocanol MF formulated with a gas mixture designed to maintain physical MF characteristics while accelerating bubble absorption, and dispensed via a canister system controlling density and bubble size (the Varisolve procedure). During and after the procedure patients undergo TCD monitoring of the MCA for 1 hr. Patients with detectable MCA bubbles receive intensive surveillance for microinfarction including MR with diffusion-weighted imaging at 1, 7 and 28 days, neurological exam, perimetry, and cardiac markers. TCD and MRI are assessed by blinded central reviewers. Recruitment will continue until 50 patients with MCA bubbles during the procedure are evaluated (projected Spring 2008).

RESULTS: In patients with GSV incompetence screened for enrollment, RL shunts are diagnosed in 1/3 of patients. In shunt-positive patients treated with polidocanol MF, 90% have detectable MCA bubble emboli during the procedure, but the number of bubbles is low (maximum 13 bubbles in patient with Grade V shunt). After evaluation of 11 patients with MCA bubbles, none have developed new MRI lesions, neurological or visual field abnormalities, or elevated cardiac markers.

CONCLUSION: Patients undergoing foam sclerotherapy are commonly exposed to gas bubbles in the cerebral (arterial) circulation. A proprietary polidocanol MF with controlled density, bubble size and gas mix has not been associated with evidence of microinfarction.

2:24 PM **Abstract No. 88**

Endoveous Laser Vein Ablation Effectiveness without the Use of Epinephrine in the Tumescent Anesthetic Mixture.

S.J. Kestwick, R.I. Chen, T. Faundeen-Jones; Northwestern Memorial Hospital, Chicago, IL

PURPOSE: Endovenous laser ablation of the greater saphenous vein (GSV) is a safe procedure. One of the potential complications of this procedure is tachyarrhythmia related to the presence of epinephrine routinely contained in the tumescent anesthetic mixture. The epinephrine in the tumescent mixture causes vasoconstriction of the treated vessel, improving transmission of the thermal energy to the vessel wall, and thus increasing the likelihood of a successful ablation procedure. We tested the hypothesis that endovenous laser ablation of the GSV can be effectively performed without the use of epinephrine as a component of the administered tumescent anesthetic, thereby potentially improving the safety profile of the procedure.

MATERIALS AND METHODS: Two independent operators performed 400 endovenous laser ablation procedures of the GSV for symptomatic venous insufficiency, using identical technique except for the presence or absence of epinephrine in the tumescent mixture. All patients were seen in follow up at 4-6 weeks after the procedure. Clinical success was defined as substantial improvement or complete resolution of the original symptoms, as determined by the patient. In those patients without significant or complete symptom resolution, duplex ultrasound was performed. Those patients found to have a completely ablated GSV were considered to have had a technical success. Those with persistent flow demonstrated within the treated vessel were considered to have had an ablation failure. We compared success rates between using and not using epinephrine with Fisher's Exact test. Statistical significance was judged at the $p < 0.05$ level.

RESULTS: Of the 250 patients who underwent ablation with the use of epinephrine in the tumescent anesthetic, 3 were found to have had an ablative failure. Of the 150 patients who underwent ablation without the use of epinephrine in the tumescent mixture, 0 were found to have ablative failure.

CONCLUSION: Endovenous laser ablation of the GSV can be effectively performed without the use of epinephrine in the tumescent anesthetic mixture. The absence of epinephrine as a vasoconstrictive agent in the tumescent mixture does not appear to adversely effect procedural success.

2:36 PM **Abstract No. 89**

Embolization of Ovarian and Internal Iliac Veins as Coadyudant Treatment of Recurrent Varicose Veins of Lower Limbs.

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PURPOSE: To show our experience with internal iliac and ovarian veins embolization 1) as coadyuvant treatment of recurrent varicous veins (RVV) in lower limbs after surgery and sclerotherapy. 2) As option of treatment of perineal varicous veins (PVV).

MATERIALS AND METHODS: We enrolled prospectively women (one year period) with RVV in lower limbs with pelvic tributaries clinically suspected and demostrated by Doppler ultrasound associated or not to PVV. We made direct venography of the ovarian and internal iliac veins looking for conections between them and RVV in the lower limbs. Those ovarian and/or internal iliac veins with proved conections with RVV in the lower limbs were embolized with coils and sclerosant agent (Morrhuate Sodium). Three